

The Pathological-Anatomical Institute of the University of Basle
(Director: Prof. Dr. A. Werthemann)
Under the Direction of Prof. Dr. F. Roulet

Sympathoblastoma in Adults with special Emphasis on its Differential Diagnosis

Inaugural-Dissertation

zur Erlangung der Doktorwürde der Medizinischen Fakultät
der Universität Basel

vorgelegt von

S. MARTIN BRONSON

aus Brockton, Mass. (U.S.A.)



19

53

Verlag von S. Karger in Basel

Hutchinson (1907) published ten cases of adrenal neuroblastoma in children where the metastases occurred to the skull, long bones and vertebrae. An adrenal tumor was found in only six cases on the left side. *Thompson* (1942) found that the characters of both types are found in many of the cases, and that too, very often the salient features are absent. In the literature the cases which showed a considerable overlapping of various criteria were listed as "unclassified", and about twenty per cent fall into this category. *Karsner* (1942) came to a similar conclusion, that the distribution of the metastases does not depend upon which adrenal is primarily affected and that there is nothing to indicate that the cytological character of the tumor has any influence on metastases.

It is therefore interesting to observe that the clinical and anatomic-pathologic findings, so varied in the infant and child, is in general even more complex with the adult in so far as the site of origin of the primary tumor and the localisation of the deposits is concerned. In the present series only one adult case would correspond to the *Hutchinson* type with metastases to the calvarium and long bones; we found eight cases with liver neoplasms, of which only five cases with lymph node metastases, coming from primary tumors having different points of origin (pleura, adrenals, etc.).

In the thirty adult cases collected in this series from the literature and in the one new case seventeen sympathoblastomas took their origin in the adrenal glands; in eight cases both adrenals were the site of various sized tumors. Nine were situated in either the left or right adrenal gland. Four of the tumors originated in the sympathetic trunk or the coeliac ganglion (one case). Three originated in the intestinal tract: stomach and small intestine; two of the cases (*Davis*) in the mediastinum. One primary tumor arose in the right pleura! (*Mendl*), while another in the inguinal lymph nodes (diagnosed by surgical biopsy and positive tissue culture results) (*Murray* and *Stout*); in another, the site of origin presented a multiple involvement of the genito-urinary organs, retroperitoneal and pelvic nodes (*Murray* and *Stout*). In two of the cases (*Maruyama*, 1941 and *Schott*, 1935) the location of the tumor is not given. A perusal of the table gives an impression of how unsystematically the various metastases were distributed in practically all possible organs of the body. For example in three of the cases there were metastases to the heart as also in our case (*Evangelisti*, *Doane* and *Solis-Cohen*, and *Davis*). Primary tumors as well as metastases in the stomach and other parts of

the intestinal tract were found in six of collected cases and in our own case. The central nervous system was the site for deposits in only three cases, *Meltzer*, *Noetzel* and *Verocay*, where nodules of varying size were found either in a cerebral hemisphere or the brain stem.

Case Report

A 59-year-old female in a weak condition, pale and somewhat adipose, arrived at the Medical Clinic of the University Hospital of Basle³, Aug. 2, 1950, with very bad, lower back pains. The suspicion of a cerebral tumor arose in the discussion with the treating physician. Diagnosis upon admittance was tentatively that of polyneuritis of undetermined origin. Anamnestic: at 10 years of age a pneumonia with pleurisy; as a sequel to this affection a cavernous tuberculosis of the lung (?) which supposedly healed after a few months (?). Since the age of twenty severe back pains; from that time recurrences over the following years, localised between both scapulas and the sacral region. At 49 years a strumectomy. Six weeks prior to admittance recurrence of severe pains in whole of back with a stabbing sensation in right scapula. Then pains in right arm and shoulder made their appearance, later extending to both legs. Two days before hospital admittance right-sided facial paralysis. At times vomiting after meals. Status upon entry into hospital: Heart sounds regular and very faint but with no pathological murmurs. Blood pressure: 137/75. Auscultation: normal breath sounds. Neurological examination: slight stiffness of neck, tongue deviates to the right. Diminution of strength in both arms and in right leg. Knee jerks fail both sides. Right facial nerve paralysis of peripheral type. Vibratory sensibility over both tibial and right ulnar bones distinctly reduced. Laboratory findings: Blood sedimentation rate on Aug. 3 is 14/36 (Westergren). Lumbar puncture: cell count of 310/3 cells, the majority lymphocytes; glucose 58 mg%, Pandy ++. Nonne, negative. Protein, 1 g/100. Pressure of spinal fluid: 16/7. Queckenstedt: physiologic or normal. Blood Wassermann, negative. Clinical diagnosis: lymphocytic meningitis (?).

Clinical course: Progressive deterioration. On the 8th of Aug. an abducens paralysis is noted on both sides and a right-sided hypoglossus paralysis; the patellar and ankle jerks fail on both sides. A severe paraesthesia of both arms and a neuralgia in shoulders and back. The hematological examination of Aug. 8th: Hgb. 97%, Erythrocytes 4.62 mill., Leukocytes 12,150. Color index 1.05.

Differential blood count: Neutrophils	79%	
Stab cells	0.3%	
Eosinophils	2.7	
Basophils	1.0%	The platelets slightly increased. Some anisocytosis.
Lymphocytes	8.7%	
Plasmacytes	0.3%	
Monocytes	7.7%	

³ I should like to take this occasion to thank Prof. Dr. H. Staub for his kindness in placing at my disposal the clinical history of the case and allowing me to publish abstracts thereof.

On Aug. 12 rapid breathing sets in, also a tachycardia of about 110, but no signs of cardiac insufficiency. Bacteriological examination of the blood culture and spinal fluid gave no pathologic agents; agglutination for various *Leptospira* negative. Aug. 14: Patient progressively worse: dyspnoea, cyanosis. Paralysis of both arms and legs. Tendon and periost reflexes extinct. On Aug. 15 patient dies in sudden collapse.

Autopsy: The body of a well-nourished, elderly, adipose woman 165 cm. long and weighing 55.2 kg. *Heart*: In the left and right auricle small subendocardial petechiae. Endocardium of the left auricle, which is somewhat dilated, is of very firm consistency and a remarkable whitish color. The cut surface of the myocardium shows numerous whitish, irregularly shaped, cicatricial formations the size of a small pea. The myocardium itself is of a brownish color. *Lungs*: Right lung. In the neighborhood of a large upper bronchus a cherry-sized pale red nodule, soft in consistency and not sharply demarcated. The hilum lymph nodes are of normal size; one contains some calcium deposits. Left lung. Situated centrally in the lower lobe is a large cherry-sized nodule of the same reddish, hemorrhagic, soft tissue. Hilum lymph nodes moist, black and of normal size and consistency as are also the paratracheal, epibronchial and those at the bifurcation. *Spleen*: is extraordinarily small (15 g). The cut surface shows a markedly developed lymphatic apparatus. The trabecular structure is not hyperplastic. *Liver*: of normal size; has thin smooth capsule. The lobular structure is somewhat irregular. The gall-bladder, of hen's egg size, has a thickened wall (1 cm.) of a very firm consistency. The tissue of the wall continues infiltratively into the liver parenchyma, and there becomes somewhat softer and reddish. *Right adrenal*: of large walnut size; cortex and medulla are not to be distinguished from one another. Upon section the tissue is homogeneously pale and red and of a soft consistency. The adrenal is, nevertheless, sharply demarcated from the right renal capsule. *Left adrenal*: is replaced by an oval-shaped, orange-sized mass that lies on the left kidney leaving the renal fibrous capsule intact. The tumor is of the same character upon section as that of the right adrenal, with in addition many soft hemorrhagic foci. In the upper pole of *right kidney* an area 3 cm. in diameter, pale red, soft and moist, being rather sharply set off from the remaining parenchyma. The pelvis is not touched by the above process. *Left kidney*: no pathological focus. *Right ovary*: is replaced by a plum-sized nodule of smooth surface, which on section shows a pale red, somewhat soft, moist tissue. Left ovary: a normal involution and firm. In the recto-uterine excavation are tiny nodular thickenings of the peritoneum. On the mucosa of the transverse colon near the gall-bladder fundus is a flat ulcerous area of about 3 cm. in diameter with irregular edges. Intestinal mucosa is in general well preserved; but in another region, the lower ileum, there is found another focus, in part ulcerous, in part roughly nodular, irregular in form and of the same size as the ulcer above. In the duodenum are numerous punctiform hemorrhages. *Calvarium* and base of the skull free of pathologic changes. Hypophysis of normal size. Meninges are of a milky-white color over the cerebral convexity; meningeal vessels filled with considerable blood. Some of the cerebral gyri, especially in the frontal lobe are flattened. The cut section shows no pathologic changes. Cerebellum, medulla oblongata and pons also show increased superficial, vascular hyperemia; here, as in the spinal cord, no pathologic changes. The vertebral column and its bone marrow are not remarkable. The ribs are also free of metastases. The medulla of the femur shaft is pale red and abundant.

Microscopic Examination

Adrenals: In general the structure is homogeneous. There are two characteristic types of tumor elements represented here: the first are the small round or oval lymphocyte-like cells with a nucleus (5.5–6.0 μ) rich in chromatin, surrounded by a very thin fringe of cytoplasm; these are the least differentiated elements or sympathogonia. The second cell type, much more numerous, is a large cell (14 to 15 μ) with polygonal-shaped nucleus containing much less chromatin, which is loosely arranged and vacuolar, while the amphophil-staining cytoplasm is broad and of irregular outline sending out long protoplasmic extensions. These cells represent the more highly differentiated sympathoblasts (see fig. 1). There is another cell type somewhat smaller than the latter with many

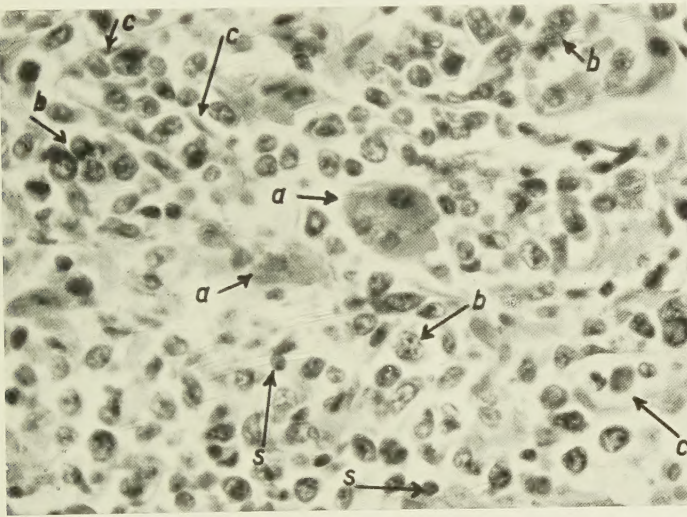


Fig. 1. The right adrenal gland. Degenerated epithelial elements of the cortex (a); in the rest of the field a diffuse tumor cell (b) infiltration, also invading the vessels (c). Sympathogonia (s) but majority of cells are sympathoblasts. Van Gieson. 550 $\times$ linear.

eosinophilic granules in the cytoplasm; they almost resemble eosinophilic myelocytes. There are also elements having a lobed nucleus, recalling the megakaryocytes. All these cells lie close by another, and as for forming any particular structure, they tend to orient themselves in parallel strands and especially to group themselves about the many small capillaries thus forming "pseudorosettes", best seen in the Giemsa stain; there are no true rosettes or *Markballen* to be seen. All the tumor cells lie in a delicate mesh of reticulum fibres which form septa or the framework in which the tumor cells lie about loosely. These fibres stain black with the various silver stains employed (*Feyrter, Rogers, etc.*) and a light yellow with the van Gieson, thus establishing their nature as reticulum fibres and not connective tissue or precollagenous reticulum. Impressive is the large

number of mitoses. A plenitude of capillaries exists into whose lumina the tumor elements have infiltrated and formed cell-plugs. Hemorrhagic as well as necrotic areas are seen. Practically nothing remains of the adrenal tissue itself except for large elements rich in protoplasm which send extensions out from several cell poles. These are the adrenal cortical elements (fig. 1).

In the several special nervous tissue stains one observes no nerve fibre prolongations of the sympathoblasts (Herxheimer, Rinschied); this is consistent with the stage of the tumor, it being in this case a primitive rapidly growing, undifferentiated sympathoblastoma. The formation of nerve fibres is characteristic of the more differentiated neuroblastic elements, as is also the formation of rosettes (*Landau*). The microscopic finding is the same in both adrenals.

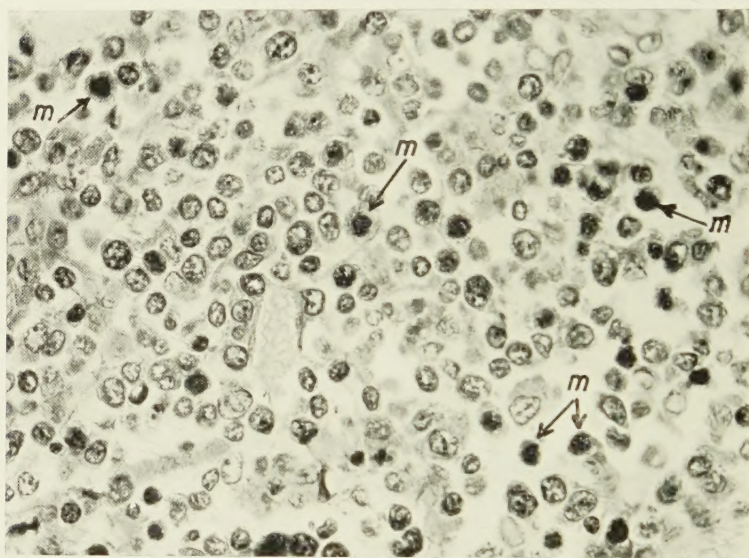


Fig. 2. The tumor of the ovary is composed of smaller cells with a darker oval or polygonal nucleus and of larger vesicular cells. Note the many mitoses (m). 550 $\times$ linear.

Liver: the first signs of infiltration are in the portal spaces, consisting of loosely lying agglomerates of small lymphocyte-like cells, sympathogonia, along with relatively few sympathoblasts. In the liver capillaries are some large round cells with eosinophilic granula (positive oxydase reaction). Some of the parenchymal lobules undergo disintegration only at their periphery near the portal space; an active tubular regeneration also takes place. The histological picture is the same as in the adrenals. Gall-bladder: penetrated by the same tumor elements. *Pancreas cauda:* same tumor cells as in the adrenals. Remarkable are the many mitoses and the loose infiltration of the fatty tissue,

in many places hardly disturbing the normal structure but in others causing its disintegration (Evangelisti). *Right ovary*: same cytological elements as in the adrenals. Many mitoses (fig. 2). A diffuse penetration of the entire stroma of the atretic follicles. The massive infiltration of the arteries and veins of various calibre seems to take place from the intima first, in the manner of a leukemia; but there are certainly many elements that penetrate the walls from the adventitia where the adjacent lymphatic channels and capillaries are completely filled by deposits (fig. 3). Here again some oxydase positive cells resembling myeloid forms containing eosinophilic granules.

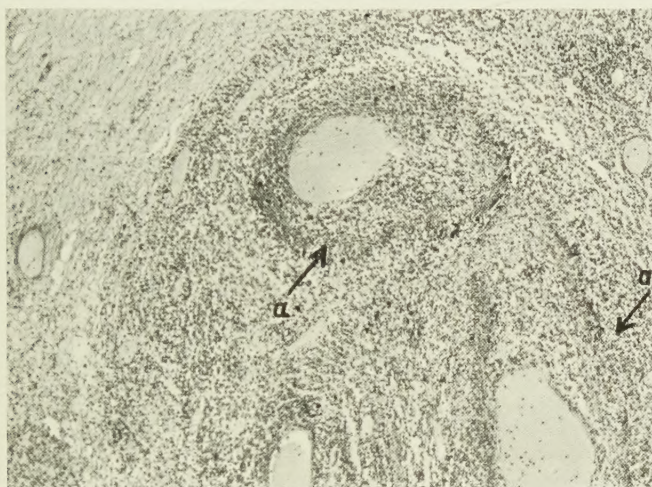


Fig. 3. Neoplastic infiltration of the vessels in the ovary (a). Van Gieson. 65 $\times$ linear.

Medulla of the femur: a mixed medulla composed of scattered lymph follicles, all the myeloid and erythroblastic series being represented. The promyelocytes are markedly well developed with plentiful eosinophilic forms. Megakaryocytes are present. On the whole the medulla is definitely hyperplastic but without any myeloid transformation (fig. 4). The tumor cells are large with a vesicular polygonal nucleus (14 μ) and a rather small irregular fringe of cytoplasm with no granules. The lymphocytes are distinguished from the tumor elements in that the latter have a much looser nuclear structure containing dispersed chromatin clumps. *Lymph nodes*: the structure of the nodes surrounding the portal vein is on the whole well preserved. The follicles are of normal size; the medullary sinuses clear. Some irritation of the reticulum cells is seen in the rather large forms. No tumor elements can be detected with certainty. The same histological structure presents itself in a paraaortal node. *Spleen*: the follicles are somewhat loosely delimited; the pulpa, rich in blood, contains some iron. In the follicles are many younger elements of the lymphatic series. Numerous eosinophil granular cells especially in the pulpa; these

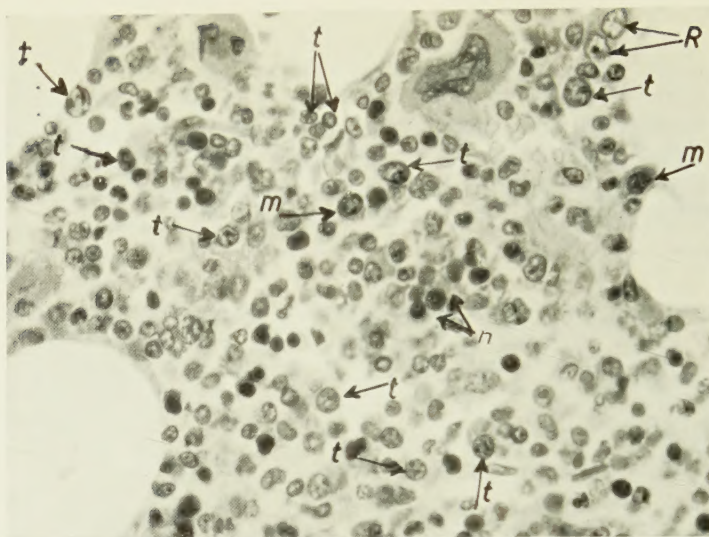


Fig. 4. Diffuse intermingling of the tumor cells (t) with the hematopoietic elements of the bone marrow. Myelocyte (m). Normoblast (n). Reticuloendothelial cells (R). Van Gieson. 550 $\times$ linear.

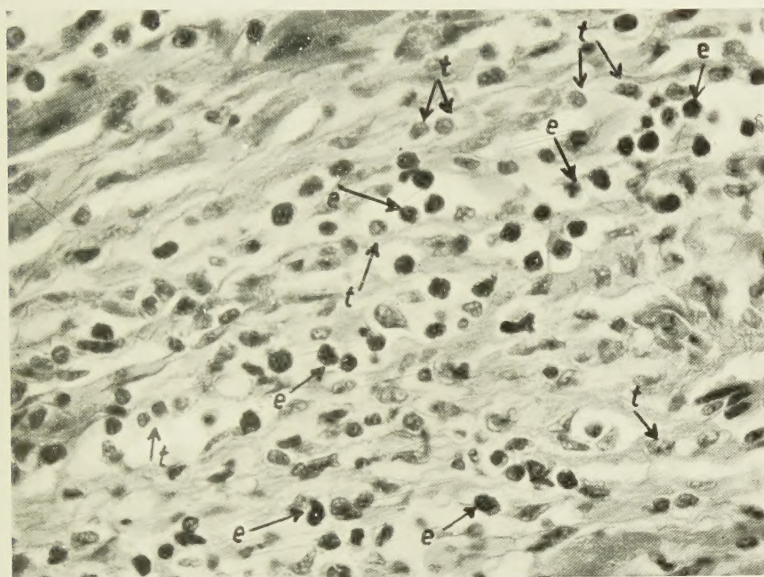
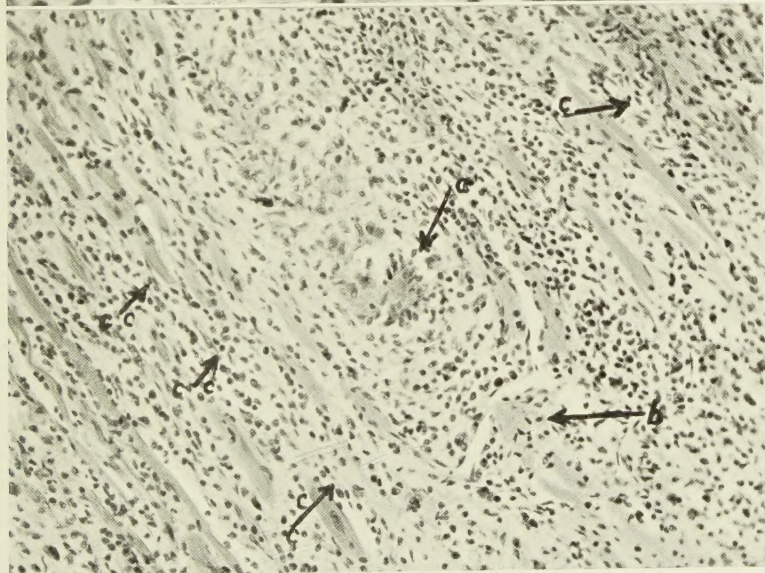
latter have the same morphology as in the above-mentioned infiltrations. *Left kidney.* the nodule seen macroscopically is infiltrated with cells that are of somewhat smaller calibre than described in the other tumors. They are more irregular in form. Near lymphocyte-like round cells one finds elements with oval, long nuclei. On the whole the impression is that of leukemia. The cells surround the tubuli thickly, destroying them gradually. Some elements of the infiltration contain eosinophilic (oxydase positive) granules. *Right kidney:* the same infiltrative character but extending over a much greater area of renal parenchyma. The cytology resembles completely that of the adrenal tumor. It is notable that very little destruction of tubuli takes place. The renal pelvis is also infiltrated. *Lungs:* a pneumonia with fibrin-filled alveoli together with tumorous infiltration, the latter in the process of necrosis. Infiltration of the alveolar walls, the large vessels

Fig. 5. Profuse infiltration of the myocardium with eosinophilic leukocytes (e). Unfortunately no colored plate could be printed so that the eosinophilic granules here appear black.

Tumor cells (t). Hämalaun-Eosin. 550 $\times$ linear.

Fig. 6. *Myocardium.* Infiltration of the tumor with dissociation of the muscle fibres. In the center is a rosette-formed granuloma (a). Degenerating muscle tissue with an epitheloid, mesenchymal reaction (b). The cells present in the infiltration are in part tumor cells, in part round cells of mesenchymal origin, among others numerous eosinophilic leukocytes. Neoplastic infiltration (c). Van Gieson. 200 linear.

and especially the perivascular lymph channels. *Transverse colon*: an unspecific ulcer. Inflammatory process and tumor cells lie side by side. On the bottom of the ulcer as also in the submucosa a small number of lymphocyte-like cells, somewhat autolysed (sympathogonia?) and a few eosinophilic leukocytes. Rarely does an inflammatory process

*Fig. 5**Fig. 6*

Year	Author	Sex	Age	Site of primary tumor	Metastases	Cell type	Diagnosis
1880	<i>Marchand</i>	♂	37	Both adrenals	Rt. brachial plexus, left sciatic nerve, rt. sup. cerv. ganglion, plexus coeliacus.	Lymphocytic cells, polygonal cells with pale nuclei and processes.	Original Diagnosis: Sarcoma Reclassification: sympathetic neuroblastoma ¹ .
1905	<i>Küster</i>	♂	34	Left adrenal	None.	Lymphocytic cells, multinucleates, some neuroblasts, rosettes.	Orig. Diag.: Glioma. Reclassif.: Sympathetic neuroblastoma.
1908	<i>Verocay</i>	♂	31	Multiple origin: adrenal, lumbar nerve, brain stem.		"Transitional cells", non-medullated fibres.	Orig. Diag.: Neurinom. Reclassif.: Neuroblastoma sympathicum.
1921	<i>Barneville</i>	♀	37	Rt. adrenal.	Both ovaries, left lung.	Fibrillae, Sympathogonia, sympathoblasts.	Sympathogonioma maturing toward sympathoblastoma.
1922	<i>Ferrero</i>	♀	61	Small intestine.	Liver.	Large, medium and small cells, round, with an eccentric vesicular nucleus, collagenous fibres.	Malignant neuroblastoma.

¹ The reclassification on this and following table are from *Scott, Oliver and Oliver (1933)*.

Year	Author	Sex	Age	Site of primary tumor	Metastases	Cell type	Diagnosis
1924	<i>Gravier and Bernheim</i>	♂	47	Both adrenals.	Tracheobronchial nodes in sup. mediastinum, rt. recurrent nerve.	Symphathogonia, sympathoblasts, rosettes, epidermoid cells.	Orig. Diag.: Parasympathoma. Reclassif.: Sympathoblastoma.
1925	<i>Ritter</i> ²	♀	55	jejunum.	None.	Symphathogonia, Sympathoblasts, rosettes, neuro-fibillar network.	Neuroblastoma.
1926	<i>Meltzer</i>	♂	40	Both adrenals.	Rt. kidney, left lung, cerebrum, mediastinal nodes, liver.	Small dark cells.	Neuroblastoma.
1926	<i>Meltzer</i>	♂	53	Rt. adrenal.	Huge liver, lymph nodes, right lung.	Small dark cells. Mitoses.	Neuroblastoma.
1927	<i>Capaldi</i>	♀	44	Under left adrenal.	Both inf. cerv. ganglia.	Symphathogonia, round dense cells with syncytium of fibres, some larger cells.	Symphathogonioma maturing toward a sympathoblastoma.
1928	<i>Blumensaat</i>	♂	47	Both adrenals.	Para-aortal lymph nodes, Epididymis, Spermatic cord, lung, kidney, hypophysis.	Symphathogonia, sympathoblasts, rosettes, semicircle and cords of cells (few ganglion cells).	Symphathogonioma.
1929	<i>Crossen</i>	♂	37	Left adrenal.	Stomach, pancreas, subcutaneous, tibia and all lymph nodes.	Round cells, rosettes, some chromaffin cells.	Orig. Diagn.: Neurocytoma. Reclassif.: Sympathoblastoma.

² This is one of the two cases of neuroblastoma published by *Ritter* together; the other case, as mentioned in the text, is unconvincing.

Year	Author	Sex	Age	Site of primary tumor	Metastases	Cell type	Diagnosis
1932	Amos	♂	55	Jejunum.		Sympathoblasts, nerve fibres.	Neuroblastoma.
1935	Eschscholtz	♂	69	Both adrenals.	Liver, right atrium of heart, stomach.	Lymphocyte-like cells, polygonal cells, giant foam cells, pseudorosettes.	Sympathoblastoma.
1936	Schoth (Dietrich, Siegmund)	♂	Alters Individuum			Symphathogonia, sympathoblasts, glia cells.	Neuroblastoma sympathicum.
1937	Barnett	♂	27	Right adrenal.	Skull, dura mater, liver, vertebrae, ribs, sternum, both lungs.	Symphathogonia, sympathoblasts, rosettes.	Neuroblastoma sympathicum.
1937	Boam and Sales (Golan)	♂	62	Both adrenals.	Rt. auricle of heart.		Neuroblastoma sympathicum.
1937	Mendel	♂	37	Rt. pleura.	Bronchus, Abdominal aorta, pancreas, sacral lymph nodes, liver, left kidney, and bladder.	Sympathoblasts, rosettes.	Malignant neuroblastoma.
1938	Noetzel	♂	52	Left adrenal.	Cerebrum, stomach, intestines, left uter, inguinal lymph nodes.	Symphathogonia, sympathoblasts, large cells with melanin pigment.	Melanin producing sympathoblastoma.

Year	Author	Sex	Age	Site of primary tumor	Metastases	Cell type	Diagnosis
1940	<i>Butz</i>	♂	25	Rt. adrenal.	Liver, portal and paraaortal lymph nodes.	Sympathoblasts, Sympathogonia, (Melanin containing cell), sympathetic ganglion cells.	Sympathoblastoma.
1940	<i>Kati</i>	♂	63	Left adrenal "pigeon-egg" sized tumor.	—	Sympathoblasts.	Sympathoblastoma.
1941	<i>Maruyama</i>	♂	66	Right adrenal	Liver, lung, mesenteric and supraclavicular nodes.	Small round cells, rosettes.	Sympathogonioma.
1942	<i>Nota</i>	♂	50	Both adrenals.	Rt. nervus trigeminus, nervus ischiadicus.	Sympathogonia, Sympathoblasts.	Neuroblastoma sympathicum.
1942	<i>Chiovenda</i> and <i>Majocchi</i>	♀	63	Pyloric antrum.	—	—	Neuroblastoma sympathicum.
1947	<i>Davis</i>	♂	65	Tumor mass in mediastinum, super. vena cava surrounded.	Tracheobronchial lymph nodes, skin over chest.	Sympathoblasts, rosettes.	Neuroblastoma sympathicum.

Year	Author	Sex	Age	Site of primary tumor	Metastases	Cell type	Diagnosis
1947	<i>Davis</i>	♂	23	Mediastinum: rt. cardiac auricle, rt. lung, pleura, diaphragm, mediastinal and periaortic lymph nodes, liver.		Cells with large, pale, elongated to round nuclei, rosettes.	Neuroblastoma sympathicum.
1947	<i>Murray and Stout</i>	♂	33	Left inguinal lymph nodes.	-	Sympathoblasts.	Sympathoblastoma.
1947	<i>Murray and Stout</i>	♂	59	Multiple: seminal vesicles, bladder wall, prostatic bed, pelvis and retroperitoneal nodes.		Rounded to slightly elongated hyperchromatic cells, pseudorosettes.	Sympathoblastoma.
1948	<i>Hawksley</i>	♂	51	Coeliac ganglion.	Lungs.	Rosettes.	Primary neuroblastoma.
1949	<i>Weber</i>	♀	60	Sympathetic plexus (level of Th ₁₀₋₁₂).	-	Sympathogonia, Sympathoblasts.	Sympathoblastoma.
1951	<i>Author's case</i>	♀	59	Both adrenals.	Lungs, heart, kidneys, pancreas, liver, ovary, small and large intestine, bone marrow.	Sympathogonia, sympathoblasta eosinophilic myelocytes and eosinophilic leukocytes, granulomas in myocardium.	Sympathoblastoma.

penetrate into the submucosa and the musculature destroying the latter so profoundly as here; the muscle fibres are being replaced by connective tissue. A tuberculosis can be ruled out. *Ileum*: The same cytology as in the ovary and pancreas, but somewhat resembling a leukemic infiltration, with fewer inflammatory elements here than in the colon.

Myocardium: A diffuse infiltration of the heart muscle takes place made up in part of cells corresponding to those already seen. The dissociation and atrophy of many muscle fibres is observed, around which very primitive undifferentiated cells lie, so that here and there nodular "granulomas" arise. There are some giant cells with an abundant cytoplasm. Innumerable eosinophilic elements, in part lobed like eosinophils of the blood stream, are found (fig. 5). The giant cells often stand in close contact with cytoplasmic extensions coming from the "regenerated" muscle fibres. On the other hand, the structural elements of the "granuloma" are furnished by the tumor. The oxydase reaction is strongly positive in relation to the quantity of eosinophilic leukocytes. The granulomas are much larger than the classical "Aschoff nodule" and contain hyalinised disintegrated muscle tissue, large histiocytes and small lymphocytes (?). Most of the time it is impossible to distinguish the lymphocytes from the tumor cells. Nevertheless here and there are small cells ($5.5\ \mu$) with hyperchromatic nuclei resembling the tumor cells elsewhere. Some of the granulomas are rosette-formed (fig. 6). *Central nervous system*: Presents no pathologic changes.

Discussion

The clinical symptoms in all the cases collected from the literature are too varied and unspecific to permit one to list essential and characteristic ones. The symptoms in this new case were on the whole misleading since they pointed to a process in the central nervous system. In most cases the posing of a clinical diagnosis is utterly impossible; the all important sign of an abdominal tumor in the region of the adrenal or the sympathetic chain can lead one only to suspect a sympathoblastoma. In this case the abdominal tumor escaped the careful examination of the clinician, understandably since the left adrenal tumor is only of orange size. A femoral and sternal puncture would probably have furnished some valuable information, perhaps the typical mosaic formations of the sympathoblasts in the bone marrow (*Kato and Wachter, 1938; Hooft and Campenolle, 1942*). These bone marrow punctures have already led to the correct diagnosis in several cases of infants and children (*Undritz*).

If the suspicion of sympathoblastoma arises in an adult there is also the valuable tissue procedure of biopsy material described by *Murray and Stout (1947)* which enabled them to make the correct diagnosis in two adults (see tables for cases). This method allows one to distinguish the sympathoblasts from lymphocytes, lymphosarcoma and small celled carcinoma because of the elective sympathoblast behavior in presence of neutral red, the formation of marginal necrosis by the neurogenic elements and, last, the production of neurites in twenty-four hours by the sympathoblasts. Since there are no

common denominators in the clinical symptoms, we are forced to depend solely on the above-mentioned diagnostic examinations, upon the anatomical and histological findings.

Anatomically the finding of a bilateral adrenal tumor speaks in itself very strongly for a sympathoblastoma. Other groups of tumors such as sarcoma or lymphosarcoma are to be dismissed *prima vista* here on the basis of the histological findings. Also the widespread deposits of the tumor in the various viscera of the body found in our case have already been noted by *Scott and Oliver* (1933) who pointed out that atypical metastases occur characteristically at older age levels of children. This "atypicalness" is not only true for the metastases but also for the site of origin of the tumor in adults, for in some of the cases collected they arose in such viscera as the pleura, stomach and jejunum (three cases). But this is only a general rule since the same phenomenon takes place in childhood: *Pick* (1912) describes a case of neuroblastoma sympathicum primary in the uterus of a two and a half-year-old female child with metastases to the ovaries. *Spreng* (1936) presents a case of a child with the primary sympathoblastoma in both adrenals with deposits to the skin, liver, and bladder. Skin metastases in infants and children have been noted often in the literature (*Klare, Debré, Bergstrom, Rupilius* and *Hepting*). The case of *Otten* is pertinent: a seven-year-old female in which a primary tumor of both adrenals metastasizes to the heart, left ovary, ileum, pancreas, duodenum, stomach mucosa, as well as kidney and bladder. In general, however, the "atypical" seat of the primary tumor and its deposits to numerous systems of organs is more characteristic of the adult cases.

In turning to the histology of the case presented, the tumor cells as already mentioned consist of the primitive, less differentiated, lymphocyte-like sympathogonial cells with dark hyperchromatic nuclei and little cytoplasm, whereas the other specific tumor elements contain a large, polygonal-shaped nucleus with loosely arranged chromatin and a broad irregular fringe of cytoplasm (sympathoblast or a more differentiated neuroblast); the latter cell is in most areas definitely preponderant thus justifying the designation of sympathoblastoma. No rosettes are formed in the primary tumors or in any of the metastases ⁴.

The appearance of other elements intermingled with the neoplastic

⁴ The absence of rosette-formation was found in the following cases of sympathoblastoma in adults collected from the literature: *Capaldi* (1927); *Meltzer* (1926), two cases; *Evangelisti* (1935); *Weber* (1949); *Murray and Stout* (1947), two cases, and *Nota* (1942).

cells, that is, large cells with eosinophilic cytoplasm, to be found in the tumors of the adrenal, pancreas, liver, ovaries, etc., remind one of eosinophilic myelocytes; but in the colon, ileum and myocardium present a structure very similar to the eosinophils of the blood. These elements with their strongly positive oxydase reaction make one consider, as coming into question, an aleukemic leukemia. But a closer examination of the bone marrow shows no pathological hyperplasia of the granulocytic elements but rather a normal hematopoietic structure in which all the various cell series are represented and none are crowded out by the other. Let us consider the blood smears: although theoretically in presence of an aleukemic leukemia one need not have an abnormal leukocyte count, it is however the rule that only a proliferation or metaplasia of the granulocytic series, localised in the tissues themselves, takes place during the so-called transitory phase. After this, sooner or later the peripheral blood is flooded with white cells. Even before this happens abnormal types of leukocytes are found in the blood (*Boyd*) although the total leukocyte count remains normal. An elevation of the total leukocyte count in the present case is noted in the three determinations made, amounting to about 12,000 in each instance; but no pathologic cell forms are seen in the blood smears. Also the fact that there exists no anemia here is uncharacteristic of a myelogenous leukemia: the erythrocytes 4.6 million, hemoglobin 97%. One of the main points against the diagnosis of leukemia is the behavior of the spleen; it is atrophic (15 g.) and does not show any evidence of leukemic transformation.

Again, the loose and infiltrative manner of penetration of the metastases in the various organs such as the ovary, kidney, liver, and capsular fat of the pancreas, for example, is not at all an unusual behavior for the sympathoblastoma, since it has been reported by other authors (*Evangelisti, Butz*).

Here, on the contrary, there is not sufficient evidence to assume a metaplasia of tissue in the various organs; it is more reasonable to admit the production of a strong, constant irritation on the bone marrow. Thus the many eosinophilic granular cells both of a structure resembling myelocytes (ovary, adrenal, etc.) and those recalling the eosinophil leukocytes of the peripheral blood (heart, jejunum and colon) can be considered as taking their origin in the bone marrow. It is remarkable that no myelocyte-like elements are seen in the colon, jejunum and myocardium. The existence of a leukemia here alongside a sympathoblastoma is dismissed as untenable.

Thus we assume that the presence of the eosinophilic cells is only of a secondary nature and is not to be considered as of equal or primary importance as tumor elements. *Wegelin* (1909) in his publication of a ganglioneuroma cited similar cases of *Borst* (1897) and *Falk* (1907) as containing very many mast cells intermingled with the tumor cells; the latter drew the conclusion that there was an equivalent proliferation of the connective tissue and that therefore these mast cells were to be considered as forming a mixed tumor. *Wegelin* disagreed with them pointing out that a marked proliferation of mast cells takes place in many chronic inflammations and that the main emphasis should be placed on the leading role of the nervous parenchymatous elements of the tumor. Here also we would like to place the emphasis on the neuroblastic cells, sympathogonia and sympathoblasts ⁵.

Conclusions

A new case of sympathoblastoma with bilateral primary adrenal tumors and metastases to numerous organs (lungs, heart, kidney, pancreas, liver, ovary, small and large intestine) is presented. First of all, our case showed no characteristic symptoms; indeed it made the impression of an affection of the central nervous system. The anamnestic findings do not allow one to establish the time of the exact beginning or onset of the tumor and its metastasizing. The sympathoblastoma in the adult shows much more complicated relationship than those found in the younger age levels, the clinical symptoms being unspecific and general in their localisation. Then the site of origin of the primary tumor as well as the fashion of metastasizing can be lawless or atypical.

Only one case collected from the literature could be considered as of the Hutchinson type with metastases to the calvarium, ribs, sternum and vertebral column. Some twenty per cent of sympathoblastomas occurring in infancy are listed as "unclassified" (with regard to the Hutchinson and Pepper types). We found that with difficulty eight of the thirty adult cases could possibly correspond to the so-called Pepper type, that is, the rest (22) would be regarded as "unclassified". It would therefore

⁵ In this regard several cases of sympathoblastoma are found in the literature reporting the occurrence of other cytologic elements alongside those of neurogenic order such as the following: giant cells, large melanin containing cells (*Butz, Noetzel, Oberndorfer*), giant foam cells (*Evangelisti*) and epidermoid bodies (*Gravier and Bernheim*).

seem highly artificial to undertake such a system of classification here and also to serve little practical purpose.

Histologically the tumor of the adrenals and its metastases presented characteristic sympathogonia and sympathoblasts of a highly undifferentiated degree with no rosette or nerve fibre formation. The behavior of the neoplasm resembled that of a leukemia in the following respects: its loose infiltration of liver, kidney and fatty tissue, its diffuse penetration of arterial and venous structures leaving the latter in many instances anatomically intact. A special characteristic observed in the new case was the concomitant development of many eosinophilic cells alongside the neurogenic elements; the former, in some organs resemble the granulated myelocytes of the bone marrow, whereas in other organs (myocardium, jejunum and colon) definitely the eosinophilic leukocytes of the blood. Remarkable giant cells or "granulomas", larger than Aschoff nodules arise in the myocardium, some assuming the form of false rosettes. The structure of these granulomas is in part furnished by the neuroblasts.

Summary

Thirty cases of sympathoblastoma occurring in adults were found in a review of the literature and one new has been added. The clinical symptoms were found on the whole to be indefinite and misleading so that recognition of the condition is of great difficulty. The site of origin of the primary tumor as well as its mode of metastasizing were found very often to follow no particular pattern, being lawless or "atypical". Thus the classifications according to Pepper and Hutchinson of these tumors appear to be impracticable and highly artificial. The new case presents unusual interest in that the manner of metastatic infiltration of numerous organs resembles that of a leukemia; moreover, the curious development of numerous eosinophilic cells alongside the neurogenic elements renders the histological picture complex. "Granulomas" larger than Aschoff nodules, sometimes in rosette form, are observed in the myocardium.

Zusammenfassung

Eine Literaturübersicht ergibt, daß bis jetzt 30 Fälle von Sympathoblastomen bei Erwachsenen bekannt sind. Ein neuer Fall wird beschrie-

ben. Die klinischen Symptome sind derart uncharakteristisch, daß eine Diagnose meist unmöglich ist. Die Lage des Primärtumors und die Art der Metastasierung sind in keiner Weise so charakteristisch, daß man eine Einteilung in die bekannten Typen Pepper oder Hutchinson vornehmen kann; diese Einteilung hat kein praktisches Interesse und sollte aufgegeben werden. Der neue Fall ist von großem Interesse, weil seine Metastasen ein leukämieartiges Bild bieten; ferner wird er durch eine bemerkenswerte Beimengung von eosinophilen Leukozyten zu den Tumorelementen charakterisiert, die vor allem im Bereich großer «Granulome» im Herzmuskel gefunden worden sind.

Résumé

30 cas de sympathoblastomes chez des adultes ont été décrits jusqu'ici; l'auteur ajoute un nouveau cas dont l'image clinique n'était pas caractéristique et ne permit pas de diagnostic. Dans ce cas comme dans bien d'autres, les métastases sont irrégulières et ne suivent pas de règles définies, ce qui amène l'auteur à rejeter les types dits «type de Pepper» et «type de Hutchison», classification artificielle et sans intérêt pratique. Le cas décrit est intéressant par le fait que l'image histologique de certaines métastases pouvait faire songer à une leucémie. De plus, l'apparition de nombreux leucocytes éosinophiles accompagnant les cellules tumorales complique encore l'aspect histologique. Des «granulomes» plus volumineux que des nodules d'Aschoff, parfois en rosettes, ont été observés dans le myocarde.

Riassunto

Dallo studio della letteratura risulta che fin ad oggi sono stati pubblicati 30 casi di simpatoblastoma in adulti. Descrizione di un nuovo caso con sintomi clinici non caratteristici. In tutti i casi la localizzazione del tumore primario ed il modo della metastatizzazione non permisero mai di fare una distinzione esatta tra il noto tipo di Pepper e quello di Hutchinson, di modo che questa classificazione non presenta alcun interesse pratico. Il nuovo caso è caratterizzato dal fatto che le metastasi presentano un quadro leucemio con associazione di leucociti eosinofili alla sostanza tumorale, specie nella regione di grandi «granulomi» nel miocardio.

Bibliography

- V. Albertini, A., and H. Willi: *Annal. Paediatr.* 152, 129, 1938. — Barnett, J.: Neuroblastoma Sympathicum der Nebenniere bei Erwachsenen. Inaug.-Diss., Zürich, 1937. — Barnewitz: *Frankf. Zschr. Path.* 26, 317, 1922. — Blumensaat: *Virchow's Arch.* 269, 431, 1928. — Borst: *Sitzungsber. d. phys. med. Ges. zu Würzburg*, 1897. — Boyd, W.: *Text. of pathology*. Henry Kimpton, London, 1947. — Butz: *Virchow's Arch.* 306, 361, 1940. — Cames, O., and J. M. Cid: *La prensa méd. argent.* 20, 1485, 1933. — Capaldi: *Frankf. Zschr. Path.* 35, 83, 1927. — Chiovenda and Majocchi: *Tumori* 28, 343, 1942. — Crossan, E. T.: *Surg. Clin. North America* 9, 1262, 1929. — Davis, P.: *Virginia Med. Monthly* 74, 76, 1947. — Doane and Solis-Cohen: *J. Am. Med. Ass.* 109, 578, 1937. — Evangelisti, T.: *Rivista d. patol. nerv.* 46, 581, 1935. — Falk: *Beitr. path. Anat.* 40, 601, 1907. — Ferrero, V.: *Arch. per le Sc. med.* 45, 114, 1922. — Gravier and Bernheim: *Lyon méd.* 134, 223, 1924. — Hawksley, L.: Quoted by Willis, R. A.: *Path. of Tumors*, Butterworth & Co., London, 1948 (fig. 417 and 418). — Herxheimer, G.: *Beitr. path. Anat.* 57, 112, 1914. — Hooft, C., and H. Compernelle: *Monatsschr. f. Kinderheilk.* 90, 333, 1942. — Karsner, H.: *Trans. Am. Ass. of Phys.* 57, 1942. — Kati, N.: *J. Med. Assoc. Formosa* 39, 515, 1940. — Kato, K., and H. Wachter: *J. Pediatrics* 12, 449, 1938. — Klare, D.: *Zur Klinik der unreifen Sympathicus-Geschwülste*. Inaug.-Diss. Rostock, 1940. — Küster: *Virchow's Arch.* 180, 117, 1905. — Landau: *Frankf. Zschr. Path.* 11, 26, 1912. — Marchand, F.: *Virchow's Arch.* 81, 477, 1880. — Maruyama: *Gann (Japan)* 35, 27, 1941. — Meltzer, S.: *Canad. Med. Ass. J.* 16, 647, 1926. — Mendl: *Frankf. Zschr. Path.* 50, 304, 1937. — Murray and Stout: *Am. J. Path.* 23, 429, 1947. — Noetzel, H.: *Frankf. Zschr. Path.* 52, 511, 1938. — Nota, J.: *Nederl. Tijdschr. Geneesk.* 86, 2690, 1942. — Oberdorfer: *Beitr. path. Anat.* 41, 269, 1907. — Otten, H.: *Sympathogonion der Nebenniere*. Inaug.-Diss., Bonn, 1938. — Pick, L.: *Berl. Klin. Wochenschr.* 1912, Nr. 1/2. — Pick and Bielschowsky: *Zschr. f. d. ges. Neurol.* 6, 1911. — Reid, M.: *Annals of Surg.* 88, 516, 1928. — Ribbert: *Geschwulstlehre*. Berlin, 1904. — Rinschied, J.: *Virchow's Arch.* 297, 508, 1936. — Ritter: *Am. J. Path.* 1, 1925. — Schott: Quoted by Dietrich-Siegmund in *Handb. d. Spez. Pathol. Anat. von Henke-Lubarsch* 8, 1044, Berlin, 1934. — Scott and Palmer: *Am. J. Cancer* 16, 903, 1932. — Scott, Oliver and Oliver: *Am. J. Cancer* 17, 396, 1933. — Spreng, A.: *Schweiz. Med. Wschr.* 1936, 1192. — Thompson, R.: *Ann. of Int. Med.* 16, 1942. — Undritz, E.: *Ann. Paediatr.* 171, 16, 1948. — Verocay: *Beitr. path. Anat.* 48, 1, 1910. — Weber, H.: *Frankf. Zschr. Path.* 60, 228, 1949. — Wegelin, C.: *Beitr. path. Anat.* 46, 403, 1909. — Weichselbaum, A.: *Virchow's Arch.* 85, 554, 1881. — Willis, R.: *Am. J. Path.* 16, 317, 1940. — Willis, R.: *Pathology of Tumors*, Butterworth & Co., London, 1948.

